

MAY 1 4 2001

## TECH CENTER 1600/2900

which are independently the same or different, and N is an integer from at least 1 to about 100, said method comprising:

- dividing a population of solid supports having at least one type of a functional group at the surface of said solid support selected from the group consisting of consisting of CO<sub>2</sub>H, OH, SH, NH, NHR, CH<sub>2</sub>Cl, CH<sub>2</sub>Br and CHN<sub>2</sub>, wherein R is a linear C<sub>1</sub>-C<sub>1</sub> alkyl group, into M batches, where M is an integer from at least 2 to about 50;
- (b) reacting each of the M batches of solid support with a component, so that the component forms a bond with the solid support via the functional group, the component being independently protected or unprotected;
- (c) adding to each batch, prior to coupling step b), concurrently therewith, or subsequently to step b), from about 0.001 to about 0.5 molar equivalent of a spectrally distinguishable fluorophore tag uniquely associated with each component and capable of forming a bond to the solid support or to the component, wherein said fluorophore tag represents a bit of a binary code and comprises zero, one, or more than one fluorescent dye(s), said dye(s) being spectrally distinguishable by excitation wavelength, emission wavelength, excited-state lifetime or emission intensity;
- (d) recombining all of said M batches after the coupling and the tagging step;
- repeating steps (a) to (d) for N-1 times, or repeating steps (a) to (d) for N-2 times followed by repeating steps (a) to (c) once, to produce a library of compounds;
- (f) performing an assay capable of indicating that any compound in the library has a

property of interest; and

- (g) identifying the compound having the property of interest by optically interrogating the fluorophore tag(s) bound to the solid support on which the compound having the property of interest was produced, said optical interrogation being carried out without isolating the solid support of interest from other solid supports.
- 99. The method of claim 98, wherein step (e) comprises repeating steps (a) to (d) for N-1 times to produce a library of compounds.
- 100. The method of claim 98, wherein step (e) comprises repeating steps (a) to (d) for N-2 times followed by repeating steps (a) to (c) once to produce a library of compounds
- 101. The method of claim 100, further comprising recombining said M batches subsequent to the performing of the assay.
- 102. The method of claim 98, wherein the optical interrogation of the fluorophore tags comprises determining the value of each of the constituent fluorophore dyes.
- 103. The method of claim 98, wherein the fluorophore tags are attached to the solid supports by covalent bonding.

orthold the method of claim 98, wherein the

The method of claim 98, wherein the fluorophore tags comprise dyes selected from the group consisting of compounds with the following chemical names:

3-(ε-carboxypentyl)-3'-ethyl-oxacarbocyanine-6,6'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonid acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3H-benz(e)indocarbocyanine-5,5',7,7'-tetrasulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5,5'-disulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethyl-3Hbenz(e)indodicarbocyqnine-5,5',7,7'-tetrasulfonic acid

1-(ε-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindotricarbocyanine-5,5'-disulfonic acid

and are activated as acrive esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

105.

The method of claim 98, wherein the fluorophore tags comprise dyes selected from the group consisting of compounds with the following chemical names:

Optito Option

6-((4,4-difluoro-5,7-dimethyl- 4-bora-3a,4a-diaza-s-indacene-3-propionyl)amino) hexanoic acid

6-((4,4-difluoro-5-phenyl-4-bora-3a,4a-diaza-s-indacene-3-propionyl) amino) hexanoic acid,

6-((4,4-difluoro-1,3-dimethyl-5-(4-methoxyphenyl)-4-bora-3a, 4a-diaza-s-indacene- 2-propionyl) amino)hexanoic acid,

6-(((4-(4,4-difluoro-5)(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) phenoxy) acetyl) amino)hexanoic acid,

6-(((4,4-difluoro-5-(2-thienyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) styryloxy)acetyl) aminohexanoic acid, and

6-(((4,4-difluoro-5-(2-pyrrolyl)-4-bora-3a,4a-diaza-s-indacene-3-yl) styryloxy) acetyl)aminohexanoic acid,

and are activated as active esters selected from the group consisting of succinimidyl, sulfosuccinimidyl, p-nitrophenol, pentafluorophenol, HOBt and N-hydroxypiperidyl.

106.

The method of claim 98, wherein the fluorophore tags comprise dyes selected from the group consisting of compound with the following chemical structures:



107.

The method of claim 98, wherein the decoding step is carried out using multi-color fluorescent imaging or spectral analysis.

Q (108.

The method of claim 107, wherein the decoding step is carried out using multicolor fluorescent imaging in combination with spectral analysis.

- 109. The method of claim 98, wherein M is an integer from at least 2 to 25.
- 110. The method of claim 98, wherein the component is protected or unprotected at a

group which is capable of participating in a further reacting step and orthogonally protected at non-participating group(s), and wherein step (d) further comprises cleaving any protecting group of the component which is to participate in a further coupling step.

- 111. The method of claim 98, wherein the fluorophore dyes are spectrally distinguishable by emission wavelength.
- 112. The method of claim 98, wherein the fluorophore dyes are spectrally distinguishable by emission intensity, the emission intensity being distinguishable by adjusting the ratio of the relative quantities of each fluorophore dye.

The method of claim 112, wherein the ratio is 1:1, 2:1, 3:1 or 4:1.

The method of claim 98, wherein the components are independently selected from the group consisting of an amino acid, a hydroxyacid, an oligoamino acid, an oligopeptide, a saccharide, an oligosaccharide, a diamine, a dicarboxylic acid, an amine-substituted sulfaydryl, a sulfhydryl-substituted carboxylic acid, and alicyclic, an aliphatic, a heteroaliphatic, an aromatic and a heterocyclic moiety.

The method of claim 98, wherein the components comprise a saccharide, said saccharide being suitably protected D- or L-glucose, fructose, inisitol, mannose, ribose, deoxyribose or fructose.

The method of claim 98, wherein the compound of interest comprises an oligonucleotide.

The method of claim 98, wherein the compound of interest comprises an

M

114.

115.

history of the series

4

oligopeptide.

118

The method of claim 98, wherein the compound of interest comprises a oligopeptide analogue, wherein independently NH(C=O) is replaced by NH(C=O)NH, NH(C=O)O, CH<sub>2</sub>(C=O) or CH<sub>2</sub>O; NH<sub>2</sub> is replaced by OH, SH, NO<sub>2</sub> or CH<sub>3</sub>; CH<sub>3</sub>S is replaced by CH<sub>3</sub>(S=O) or CH<sub>3</sub>CH<sub>2</sub>; indole is replaced by naphthyl or indene; hydroxyphenyl is replaced by tolyl, mercaptophenyl or nitrophenyl; and/or hydrogen in an aromatic ring is replaced by chlorine, bromine, iodine or fluorine;  $C_1$ - $C_4$  alkyl is replaced by partially or fully fluorinated  $C_1$ - $C_4$  alkyl.

Who was a second

The method of claim 98, wherein the component comprises an aromatic moiety, said aromatic moiety being para-disubstituted benzene, biphenyl, naphthalene or anthracene, either substituted or unsubstituted by linear or branched chain lower alkyl, alkoxy, halogen, hydroxy, cyano or nitro.

(120 (120

The method of claim 98, wherein the component comprises an heterocyclic moiety, said heterocyclic moiety being 2,6-disubstituted pyridine, thiophene, 3-7-disubstituted –protected indole or 2,4-disubstituted imidazole, either substituted or unsubstituted by linear or branched chain lower alkyl, alkyl, halogen, hydroxy, cyano or nitro.

- 121. The method of claim 98, wherein the solid support is selected from the group consisting of a microsphere, a bead, a resin or a particle, said solid being composed of a material selected from the group consisting of polystyrene, polyethylene, cellulose, polyacrylate, polyacrylamide, silica and glass.
- 122. The method of claim 98, wherein the assay is performed while the compound is

bound to its solid support.

Wy W

- 123. The method of claim 98, wherein the assay is performed while the compound is cleaved from its solid support under conditions whereby the compound remains adsorbed to the solid support.
- 124. The method of claim 98, wherein the assay is performed while the compound is cleaved from its solid support, while the logical connection is maintained between the compound and the solid support on which it is prepared.
- 125. The method of claim 98, wherein the assay is performed by cleaving the compound from the solid support while permitting diffusion through solution and binding to a probe, said probe being arranged in proximity to each solid support.

W (126).

- A chemical library prepared according to the method of claim 98.
- 127. The method of claim \( \partial 8 \), wherein N is an integer from at least 2.
- 128. The method of claim 98, wherein N is an integer from at least 4 to about 12.

## REMARKS

Favorable reconsideration and withdrawal of the objections to and rejections of the subject application are respectfully requested in view of the amendments and remarks submitted herewith.

Claims 74 to 97 were pending in the application. By this amendment, Applicants have